Scripps research team unravels new cellular repair mechanism

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A Scripps Research team has unraveled a new biochemical pathway that triggers a critical repair response to correct errors in the DNA replication process that could otherwise lead to harmful or fatal mutations in cells. Though the work focused on yeast cells, the team expects to find an analogous system in human cells that could be exploited as a target for potential therapies for cancers, which are often caused by such repair mechanisms going off course. The research was published today in an advanced, online issue of the *Proceedings of the National Academy of Sciences*.

The cell cycle, which allows cells to replicate their DNA and produce new cells, is controlled by a complex concert of enzymes and other components. In addition there are "checkpoint" mechanisms that can block continuation of the process if something goes amiss. Via mechanisms still poorly understood, a checkpoint in the reproduction process can detect problems that interfere with DNA copying. This detection can in turn trigger several potential responses.

"If the cycle is paused because the cell is having some problem," says study lead Professor Curt Wittenberg, of the Scripps Research Departments of Molecular Biology and Cell Biology, "it can't stop and go back, so it either kills the new cell or repairs the problem."

The checkpoint mechanisms that control the cell cycle are of great interest not only because they are such a fundamental aspect of biology, but also because problems in the cycle and its DNA repair mechanisms

can lead to mutations that cause the unchecked proliferation of cells associated with various cancers.

The Wittenberg group recently identified a protein dubbed Nrm1 that appeared to play important roles in a yeast cell's successful transition from the G1 phase, in which cells prepare to replicate DNA, to actual replication during the S phase. Now, in the new paper, the Wittenberg group in collaboration with colleagues in the Scripps Research laboratories of Professors Paul Russell and John Yates show what some of those roles are.

At specific points in the cell cycle, groups of genes are turned on and off to produce the enzymes and other components needed for progression into the next cell cycle phase, and a healthy cell will only move forward into the next phase of the cycle if certain standards are met.

However, if a problem arises in the DNA replication process during the S phase, the entire process stalls.

"If either the replicating enzymes run into damage, or if there are insufficient precursors for making DNA, then this checkpoint response will be activated," says Wittenberg. "There are two aspects to this response. One is to prevent the cycle from proceeding, and the other is to prepare the cell to deal with the damage."

Wittenberg and his colleagues have found that during normal cell division, Nrm1's binding to DNA represses the activity of genes expressed during the G1 phase, in preparation for the subsequent S phase. The team has now shown that when such stalls occur, collectively referred to as DNA stress, Nrm1's repression of the G1 genes is blocked, allowing those genes to be turned back on. This presumably enables production of proteins needed to correct the problem that caused the stall.

"So, now you have cells in the S phase, which don't typically express these genes, expressing them," says Wittenberg.

The researchers were able to tease out Nrm1's specific activities through experiments where they intentionally blocked the cell cycle in yeast cells by robbing them of the precursors needed for DNA replication. They were able to show that, as a result of this induced stress, Nrm1 was chemically altered by a known checkpoint enzyme, resulting in the loss of binding to G1 genes. This resulted in expression of the G1 genes during S phase. Because those genes encode replication and repair enzymes, re-expression of the G1 genes facilitates re-starting of DNA replication.

Because the onset of cancer is so intimately tied to problems in the cell cycle, numerous cancer drugs currently under development target checkpoint mechanisms, with the goals of making cells more sensitive to chemotherapeutic agents that damage DNA, and in some cases protecting normal proliferating cells from cell cycle arrest and death. Given that, once Nrm1's human analog and its activity are identified, Wittenberg and his colleagues are hopeful the information could provide fruitful targets for new cancer therapies tied to the mechanism involved.

Source: Scripps Research Institute